DETAILED ACTION

Amendment Entry

1. Applicant's preliminary amendment filed 4/14/06 to eliminate multiple claim dependency has been acknowledged. The following action addresses all the outstanding claims. Examiner apologizes for any inconvenience this may have caused applicant.

Election/Restrictions

2. Applicant's election with traverse of Group I (claims 1-7 and 13-14) in the reply filed on 17 April 2009 is acknowledged. Applicant contends that the restriction requirement is improper because examiner did not address PCT rule 1.475. This argument was carefully considered but not found persuasive. In particular, PCT rule 1.475 is recited below and was previously addressed in the restriction requirement of record mailed 3/20/09.

37 CFR 1.475. Unity of invention before the International Searching Authority, the International Preliminary Examining Authority and during the national stage. (a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention "). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features " shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. (b) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories: (1) A product and a process specially adapted for the manufacture of said product; or (2) A product and a process of use of said product; or (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or (4) A process and an apparatus or means specifically designed for carrying out the said process; or (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process. (c) If an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present. (d) If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c). (e) The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

3. The Restriction Requirement is still deemed proper and is therefore made **FINAL.**

4. Claims 8-12 and 15-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/25/09.

Priority

5. It is noted that this application appears to claim subject matter disclosed in prior Application No. PCT/JP04/15671 filed 10/15/04 and Japan Application No.355192 filed 10/15/03. *A reference to the prior application must be inserted as the first sentence(s) of the specification of this application* or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application.

If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c).

A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional.

The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Information Disclosure Statement

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered.

7. The information disclosure statement filed 5/11/07 has been considered as to the merits before First Action.

8. The information disclosure statement filed 1/3/08 has been considered as to the merits before First Action.

Specification

9. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Sequence Non-Compliance

10. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).

However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

The specification (for example see page 12, 3rd line from the bottom) recites sequences but the actual sequence identification numbers are not included. Please provide the appropriate sequence identification numbers in order to comply with the sequence rules.

Applicant is given THREE MONTHS from the mailing date of this communication within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

I. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 is vague and indefinite because it is not clear what modification is intended in the instant claims. The claims appear to substitute amino acids, however it is not know what the term "circularly permuted" encompasses. Will the fluorescent indicator be circular? Will the N-terminal be combined with the C-terminal? Will the indicator consist of a single wild-type protein or comprise two proteins (simultaneously containing the donor and acceptor)? As recited the metes and bounds of the claims can not be determined. Appropriate correction is required.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

II. Claims 1-3 are rejected under 35 U.S.C.102(b) as being anticipated by anticipated by Tsien et al. (US Patent #6,197,928).

Tsien et al. teach a probe (col. 2, line 5.5) comprising: a target binding site moiety (col. 2, lines 14-18 and col. 2, lines 55-63) which is attached to a first fluorescent polypeptide (donor fluorescent protein moiety covalently coupled to the binding protein moiety, col. 2, lines 14-18 and lines 55-63); a mimic moiety which is capable of binding to the target binding site moiety (col. 2, lines 65-66) attached to a second fluorescent polypeptide (donor fluorescent protein moiety is covalently coupled to the binding protein moiety, col. 2, lines 14-18 and lines 55-60).

The constructs further include a linker that connects the two fluorescent polypeptides and which allow the distance between the fluorescent polypeptides to vary (col. 2, lines 55-60), the fluorescent polypeptides being so as to display fluorescence resonance energy transfer between them (donor and acceptor moieties exhibit FRET when in close proximity to each other and fluorescent indicator utilizes FRET,col. 6, lines 43-52). Tsien et al. teach that the target binding site moiety is a peptide (col. 2, lines 36-40), the mimic moiety is a peptide (col. 2, lines 53-54), the linker is a peptide (col. 2, lines 32-33) and the entire probe is a single polypeptide (col. 2, lines 66-67). In one embodiment, Tsien et al teach that the first fluorescent polypeptide is CFP (donor emits blue-green light) and the second is YFP (acceptor emits yellow-green light, col. 8, lines 35-40).

III. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsien et al. (WO 98/40477).

Tsien et al. disclose fluorescent indicators (protein sensors or probe) which are used to detect analytes.

The indicators include a binding protein moiety (mimic peptide), a donor fluorescent protein moiety (second fluorescent polypeptide), and an acceptor fluorescent protein moiety (first fluorescent polypeptide). See abstract. In one embodiment, the protein indicators also include a target peptide binding moiety which binds to the acceptor and the binding protein moiety. See figure 1 and page 11 lines 18-30.

The probe is utilized to detect FRET measurements as a result of analyte binding. For example, see page 12. The donor and acceptor fluorescent moieties can be Aequorea-related moieties, including GFP. See page 2 lines 17-20, page 8 lines 20-25, and page 16. FRET or fluorescence is measured with a fluorometer (detector) after sample excitation. See page 14 line 25 through page 15 line 11.

IV. Claims 1-6, 13, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Baird et al. (Proc. Natl. Acad. Sci., September 28, 1999, Vol.96, No.20, pages 11241-11246).

Baird et al. disclose fluorescent compositions that are indicators (protein sensors or probe) which are used to detect analytes. The indicators are constructed by circular permutation and ligand insertion. This produced enhanced yellow fluorescent GFP measurements. See abstract.

With respect to the construct containing a localization sequence, this is deemed inherent to the taught compositions.

Allowable Subject Matter

14. Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. For reasons aforementioned, no claims are allowed.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week.

In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached on (571) 272-0806.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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10/25/09

/Lisa V. Cook/
Primary Examiner, Art Unit 1641